REMARKS

Applicants have received and reviewed the Office Action mailed August 13, 2002. By way of response, Applicants have canceled claims 28 – 34 and 38 – 44, amended claims 24 – 27, 35 – 37, and 45 – 67 and added new claims 68 – 99. No new matter has been added. Claims 24 – 27, 35 – 37, and 45 – 99 are now pending. Applicants note that a declaration from Dr. P. Schlievert, referenced in the remarks below, will be submitted separately.

Applicants appreciate and acknowledge the withdrawal of rejections under 35 U.S.C. § 112(2).

For the reasons given below, Applicants respectfully submit that the amended claims are in condition for allowance, and notification to that effect is earnestly solicited.

Petition for Extension of Time

It is noted that a three-month petition for extension of time is necessary to provide for timeliness of the response. A request for such an extension is made extending the time for response from November 13, 2002 to February 13, 2003.

97.5% & 99% Identity – Basis in the Specification

Claims 68-99 are written to recite a percentage of identity with Streptococcal pyrogenic exotoxin type C (SPE-C). Basis for such claims exists in the specification and no new matter is being added thereby. The Examiner's attention is directed to examples of the specification discussing up to 6 amino acid changes being made at pages 8, 21, and 23 of the specification. Further, it is noted that the specification discloses that SPE-C is 235 amino acids in length at page 22 of the specification and also in Figure 1. Accordingly, when one calculates percentage identity using 229 amino acids that are identical (235-6) one arrives at a value of 97.45% identity, which is reasonably rounded off to 97.5%.

Examiner's attention is further drawn to pages 7 and 8 of the specification where it is disclosed that mutated toxins of the present invention preferably have up to 99% homology with wild-type SPE-C toxin.

Accordingly, there is support in the specification for claim language relating to both 97.5% identity and 99% identity with SPE-C.

Drawings

The specification has been amended to include sequence identifying numbers in the brief description of the drawings.

35 U.S.C. § 112, First Paragraph Rejections

The Examiner rejected claims 24-44, 53 and 57-67 under 35 U.S.C. § 112, first paragraph. The Office Action asserts that the claims must be limited to specifically exemplified single and double mutations. Applicants respectfully traverse this rejection.

The Office Action asserts the specification does not reasonably provide enablement for a Streptococcal pyrogenic exotoxin type C (SPE-C) mutant with three, four or five mutations at the recited positions. The Office Action goes on to reiterate this position by asserting that there are no examples that teach three, four or five substitutions at each of the recited positions, as well as making other points with respect to mutant polypeptides with three or more substituted positions.

However, the specification clearly enables mutant toxins with three or more substituted positions because it discloses both how such a mutant would be made as well as the specific locations at which the substitutions should occur. For example, the specification discloses a method of making mutants having more than two substitutions for example at p. 35, example 5. Further, the specification discusses locations for mutations by describing a mutant comprising an amino acid substitution in a β-barrel of a B-subunit or a N-terminal alpha helix. At least page 11, lines 12 - 22 of the specification supports mutations on β-barrel 4 of B-subunit 5. Particular amino acids supported as points for mutation in the β-barrels include His-35, Asn-38, Thr-33 and Leu-36. At least page 13, lines 16 - 24 of the specification supports mutations on N-terminal alpha helix 51. Particular amino acids supported as points for mutation in the N-terminal alpha helix include Ser-11, Asp-12, Tyr-15 and Tyr-17. At least page 13, line 25 through page 14, line 5 supports mutations on a central alpha helix. Particular amino acids supported as points for mutation in the central alpha helix include Lys-135, Lys-138, Tyr 139, and Asp-142. Thus, with a method of making mutant toxins with three or more substituted positions and with a disclosure that describes which specific locations should be substituted, the specification is enabling for one of skill in the art to produce mutant toxins with three or more substituted positions.

Further evidence of this enablement is provided by the Declaration of Dr. P. Schlievert which shows that the teachings of the specification can be used to create mutant toxins with three

or more substituted positions. Specifically, Dr. Schlievert has constructed triple mutants, including Y15A/H35A/N38D in accordance with the methods of the present invention that have reduced toxicity but adequate immunogenicity.

To view this point otherwise would be requiring that the claims be limited to only the exemplified embodiments. However, authority found in the MPEP and the case law, which applicant has pointed out in the parent application and which should be well known to the Examiner, indicate that it is inappropriate to limit an invention to exemplified embodiments, particularly when the application provides factual support for broader claims.

The MPEP addresses the severity of limiting claims to exemplified embodiments:

In In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

M.P.E.P. at 2164.08.

The MPEP notes that limiting an inventor to claims to preferred materials or what the inventor has found will work does not serve the constitutional purpose of promoting progress in the useful arts. In the present case, Applicants have exemplified numerous nonlethal mutants of SPE-C, have explicitly described various amino acids that are preferred sites for making such mutants, and specifically describe secondary structural features that are suitable locations for mutations eliminating toxicity. By the standard expressed in In re Goffe and in the MPEP at 2164.08, constitutional purposes would be defeated by limiting the inventor to the specifically disclosed mutants of SPE-C.

Applicants further note that the amended and newly presented claims relating to mutants of SPE-C including particular substitutions at particular amino acids is fully supported. Each of these residues are specifically called out in the present specification as preferred locations for substitutions. For example, the specification discusses a mutant comprising an amino acid substitution in a β-barrel of a B-subunit or a N-terminal alpha helix. At least page 11, lines 12 - 22 of the specification supports mutations on β-barrel 4 of B-subunit 5. Particular amino acids supported as points for mutation in the β-barrels include His-35, Asn-38, Thr-33 and Leu-36. At

least page 13, lines 16 - 24 of the specification supports mutations on N-terminal alpha helix 51. Particular amino acids supported as points for mutation in the N-terminal alpha helix include Ser-11, Asp-12, Tyr-15 and Tyr-17. At least page 13, line 25 through page 14, line 5 supports mutations on a central alpha helix. Particular amino acids supported as points for mutation in the central alpha helix include Lys-135, Lys-138, Tyr 139, and Asp-142.

The Office Action asserts that specification only provides guidance to specific amino acids and does not teach any amino acid substitution may be changed without causing a detrimental effect to the SPE-C toxin to be produced. The Office Action further asserts that the claims do not recite whether the substitution will be a conservative substitution and expresses concern over producing a stable SPE-C toxin. The issues of detrimental effect, conservative substitutions, and protein stability are all interrelated and will therefore be addressed together.

The Applicants respectfully disagree with the Examiner regarding the relevancy of detrimental effect, conservative substitutions, and protein stability for this invention. An aspect of the mutant toxins of the present invention is their ability to be immunogenic. However, detrimental effect, conservative substitutions, and protein stability are simply irrelevant. The protein does not have to remain intact to function as intended. Substitutions do not have to be conservative for the mutants to function as immunogens. There is support for claims that the mutants can be immunogenic. Four double mutants (Y15A/N38A, Y17A/N38A, Y15S/N38S, and Y17S/N38S) were prepared as described in Example 5 and then evaluated in Example 6. The mutations were effective immunogens. Finally, there are no claims in the present invention regarding the stability of the mutations. Therefore, it is believed that questioning the detrimental effect, conservative substitutions, and protein stability of the mutants is inappropriate.

Conclusion

Accordingly, it is submitted that the amended and newly presented claims fully comply with § 112, first paragraph, and withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, Second Paragraph Rejections

The Examiner rejected claim 24-67 under 35 U.S.C. § 112, second paragraph. The Office Action contends that the claims refer to amino acid substitutions without referring to a basic sequence which is being substituted. The applicants respectfully traverse this rejection.

While not conceding the correctness of the Examiner's rejection, the applicants, in the interest of moving prosecution forward, have amended the claims to recite a basic amino acid sequence that is being substituted rendering this rejection moot.

Summary

In summary, Applicants assert that each of claims 24 – 27, 35 – 37, and 45 – 99 are in condition for allowance, and notification to that effect is earnestly solicited.

The Examiner is invited to contact Applicants' undersigned representative at the telephone number provided below, if the Examiner believes that doing so will expedite prosecution of the application.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
(612) 332-5300

Date: Feb 13, 2003

Mark T. Skoog

Mark T. Skoog
Reg. No. 40,178
MTS:MED

MARKED-UP VERSION TO SHOW CHANGES MADE

In the Specification

Please replace the paragraph beginning at page 5, line 20 with the following:

Figure 1 shows the nucleotide sequence of *speC* (SEQ ID NO: 1). Numbering is in reference to the ATG start codon. Possible promoter (-10, -35) and Shine-Dalgarno (SD) sequences are noted. The deduced amino acid sequence (SEQ ID NO: 2) is given below the nucleotide sequence (SEQ ID NO: 1). An asterisk after residue 27 indicates the cleavage site between the signal peptide and mature protein. Overlined nucleotides 3' of the translation stop codon are palindromic sequences.

In the Claims

24. (Twice Amended) An isolated [mutant] Streptococcal pyrogenic exotoxin type C (SPE-C toxin) comprising:

an amino acid substitution of aspartic acid-12 of SEQ ID NO: 2, tyrosine-15 of SEQ ID NO: 2, tyrosine-17 of SEQ ID NO: 2, histidine-35 of SEQ ID NO: 2, asparagine-38 of SEQ ID NO: 2, or substitution at more than one of these amino acids; and

wherein the mutant is nonlethal compared with a wild type SPE-C toxin.

25. (Amended) The isolated [mutant] SPE-C toxin of claim 24, wherein the amino acid substitution comprises the substitution of aspartic acid-12 of SEQ ID NO: 2 to alanine, glutamic acid, asparagine, glutamine, lysine, arginine, serine, or threonine; the substitution of tyrosine-15 of SEQ ID NO: 2 to phenylalanine, alanine, glycine, serine, or threonine; the substitution of tyrosine-17 of SEQ ID NO: 2 to phenylalanine, alanine, glycine, glutamic acid, lysine, arginine, aspartic acid, serine, or threonine; the substitution of histidine-35 of SEQ ID NO: 2 to phenylalanine, alanine, glycine, glutamic acid, lysine, arginine, aspartic acid, tyrosine, phenylalanine, serine, or threonine; the substitution of asparagine-38 of SEQ ID NO: 2 to alanine, aspartic acid, glutamic acid, lysine or arginine; or substitution at more than one of these amino acids.

26. (Amended) The isolated [mutant] SPE-C toxin of claim 25, wherein the amino acid substitution comprises the substitution of aspartic acid-12 of SEQ ID NO: 2 to alanine, the substitution of tyrosine-15 of SEQ ID NO: 2 to alanine or serine, the substitution of tyrosine-17 of SEQ ID NO: 2 to alanine or serine, the substitution of histidine-35 of SEQ ID NO: 2 to alanine, the substitution of asparagine-38 of SEQ ID NO: 2 to alanine, serine, or aspartic acid; or substitution at more than one of these amino acids.

27. (Amended) The isolated [mutant] SPE-C toxin of claim 26, wherein the amino acid substitution comprises the substitution of tyrosine-15 of SEQ ID NO: 2 to serine or alanine and of asparagine-38 of SEQ ID NO: 2 to serine, alanine, or aspartic acid; the substitution of tyrosine-17 of SEQ ID NO: 2 to serine or alanine and of asparagine-38 of SEQ ID NO: 2 to serine, alanine, or aspartic acid; or the substitution of tyrosine-15 of SEQ ID NO: 2 to alanine, histidine-35 of SEQ ID NO: 2 to alanine, and asparagine-38 of SEQ ID NO: 2 to aspartic acid.

35. (Twice Amended) An isolated [mutant] SPE-C toxin comprising:

an amino acid substitution of aspartic acid-12 of SEQ ID NO: 2 to alanine, glutamic acid, asparagine, glutamine, lysine, arginine, serine, or threonine;

an amino acid substitution of tyrosine-15 of SEQ ID NO: 2 to phenylalanine, alanine, glycine, serine, or threonine;

an amino acid substitution of tyrosine-17 of SEQ ID NO: 2 to phenylalanine, alanine, glycine, glutamic acid, lysine, arginine, aspartic acid, serine, or threonine;

an amino acid substitution of histidine-35 of SEQ ID NO: 2 to phenylalanine, alanine, glycine, glutamic acid, lysine, arginine, aspartic acid, tyrosine, phenylalanine, serine, or threonine;

an amino acid substitution of asparagine-38 of SEQ ID NO: 2 to alanine, aspartic acid, glutamic acid, lysine or arginine; or

substitution at more than one of these amino acids; and

wherein the mutant is nonlethal compared with a wild type SPE-C toxin.

36. (Amended) The isolated [mutant] SPE-C toxin of claim 35, wherein the amino acid substitution comprises the substitution of aspartic acid-12 of SEQ ID NO: 2 to alanine, the substitution of tyrosine-15 of SEQ ID NO: 2 to alanine or serine, the substitution of tyrosine-17 of SEQ ID NO: 2 to alanine or serine, the substitution of histidine-35 of SEQ ID NO: 2 to alanine, the substitution of asparagine-38 of SEQ ID NO: 2 to alanine, serine, or aspartic acid; or substitution at more than one of these amino acids.

37. (Amended) The isolated [mutant] SPE-C toxin of claim 36, wherein the amino acid substitution comprises the substitution of tyrosine-15 of SEQ ID NO: 2 to serine or alanine and of asparagine-38 of SEQ ID NO: 2 to serine, alanine, or aspartic acid; the substitution of tyrosine-17 of SEQ ID NO: 2 to serine or alanine and of asparagine-38 of SEQ ID NO: 2 to serine, alanine, or aspartic acid; or the substitution of tyrosine-15 of SEQ ID NO: 2 to alanine, histidine-35 of SEQ ID NO: 2 to alanine, and asparagine-38 of SEQ ID NO: 2 to aspartic acid.

45. (Amended) An isolated [mutant] Streptococcal pyrogenic exotoxin type C (SPE-C toxin) comprising an amino acid substitution at aspartic acid-12 of SEQ ID NO: 2.

46. (Amended) The isolated [mutant] SPE-C toxin of claim 45, wherein the amino acid substitution comprises alanine for aspartic acid-12 of SEQ ID NO: 2.

47. (Amended) An isolated [mutant] Streptococcal pyrogenic exotoxin type C (SPE-C toxin) comprising an amino acid substitution at asparagine-38 of SEQ ID NO: 2.

48. (Amended) The isolated [mutant] SPE-C toxin of claim 47, wherein the amino acid substitution comprises aspartic acid for asparagine-38 of SEQ ID NO: 2.

49. (Amended) An isolated [mutant] Streptococcal pyrogenic exotoxin type C (SPE-C toxin) comprising an amino acid substitution at tyrosine-15 of SEQ ID NO: 2 and at asparagine-38 of SEQ ID NO: 2.

50. (Amended) The isolated [mutant] SPE-C toxin of claim 49, wherein the amino acid substitution comprises serine or alanine for tyrosine-15 of SEQ ID NO: 2 and aspartic acid for asparagine-38 of SEQ ID NO: 2.

51. (Amended) The isolated [mutant] SPE-C toxin of claim 49, wherein the amino acid substitution comprises serine for tyrosine-15 of SEQ ID NO: 2 and serine for asparagine-38 of SEQ ID NO: 2.

52. (Amended) The isolated [mutant] SPE-C toxin of claim 49, further comprising an amino acid substitution at histidine-35 of SEQ ID NO: 2.

53. (Amended) The isolated [mutant] SPE-C toxin of claim 52, wherein the amino acid substitution comprises alanine for tyrosine-15 of SEQ ID NO: 2, alanine for histidine-35 of SEQ ID NO: 2, and aspartic acid for asparagine-38 of SEQ ID NO: 2.

54. (Amended) An isolated [mutant] Streptococcal pyrogenic exotoxin type C (SPE-C toxin) comprising an amino acid substitution at tyrosine-17 of SEQ ID NO: 2 and at asparagine-38 of SEQ ID NO: 2.

55. (Amended) The isolated [mutant] SPE-C toxin of claim 54, wherein the amino acid substitution comprises serine or alanine for tyrosine-17 of SEQ ID NO: 2 and aspartic acid for asparagine-38 of SEQ ID NO: 2.

56. (Amended) The isolated [mutant] SPE-C toxin of claim 54, wherein the amino acid substitution comprises serine for tyrosine-17 of SEQ ID NO: 2 and serine for asparagine-38 of SEQ ID NO: 2.

57. (Amended) An isolated [mutant] Streptococcal pyrogenic exotoxin type C (SPE-C toxin) comprising an amino acid substitution at tyrosine-15 of SEQ ID NO: 2, at histidine-35 of SEQ ID NO: 2, and at asparagine-38 of SEQ ID NO: 2.

58. (Amended) The isolated [mutant] SPE-C toxin of claim 45, wherein the amino acid substitution comprises alanine for tyrosine-15 of SEQ ID NO: 2, alanine for histidine-35 of SEQ ID NO: 2, and aspartic acid for asparagine-38 of SEQ ID NO: 2.

59. (Amended) An isolated [mutant] Streptococcal pyrogenic exotoxin type C (SPE-C toxin) comprising an amino acid substitution at aspartic acid-12 of SEQ ID NO: 2, at tyrosine-15 of SEQ ID NO: 2, at tyrosine-17 of SEQ ID NO: 2, at histidine-35 of SEQ ID NO: 2, at asparagine-38 of SEQ ID NO: 2, or at up to three of these amino acids.

60. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises serine or alanine for tyrosine-15 of SEQ ID NO: 2 and aspartic acid for asparagine-38 of SEQ ID NO: 2.

61. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises serine or alanine for tyrosine-17 of SEQ ID NO: 2 and aspartic acid for asparagine-38 of SEQ ID NO: 2.

62. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises serine for tyrosine-15 of SEQ ID NO: 2 and serine for asparagine-38 of SEQ ID NO: 2.

63. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises serine for tyrosine-17 of SEQ ID NO: 2 and serine for asparagine-38 of SEQ ID NO: 2.

64. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises alanine for tyrosine-15 of SEQ ID NO: 2.

65. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises alanine for tyrosine-15 of SEQ ID NO: 2, alanine for histidine-35 of SEQ ID NO: 2, and aspartic acid for asparagine-38 of SEQ ID NO: 2.

66. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises aspartic acid for asparagine-38 of SEQ ID NO: 2.

67. (Amended) The isolated [mutant] SPE-C toxin of claim 59, wherein the amino acid substitution comprises alanine for aspartic acid-12 of SEQ ID NO: 2.

Claims 68 – 99 are new.